

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 6 of 14

RECEIVED
CENTRAL FAX CENTER

JUN 12 2008

REMARKS

I. Petition for Extension of Time

Applicants herewith petition the Commissioner for Patents to extend the time for response to the Office Action mailed 12 December 2007 for three (3) months from 12 March 2008 to 12 June 2008. Authorization is given to charge the extension of time fee of \$1020.00 (37 C.F.R. §1.136 and §1.17) to Deposit Account No. 23-1703. Any deficiency or overpayment should be charged or credited to the above numbered deposit account.

II. Telephonic Interview

On behalf of the Applicant, the undersigned Attorney wishes to thank the Examiner for the courtesy of the telephonic interview of 28 May 2008.

III. Claim Amendments

According to the Advisory Action mailed 27 March 2008, the claim amendments of 7 March 2008 were entered. In this Amendment, claim 1 has been amended to clarify the composition and structure of the claimed dosage form.

With regard to composition, the claimed dosage form comprises a core material and a semipermeable membrane. The core material comprises an omeprazole compound, one or more alkalizing agents, one or more swelling agents and, optionally, a starter seed and other pharmaceutically acceptable excipients. As disclosed in the specification at page 5, lines 19-24, the core material may be produced with starter seeds or by extrusion, spheronization or compression to have a homogenous distribution of the active and excipients. Other conventional techniques known in the art are also suitable in preparing the core material. In this regard, the Examiner's attention is directed to the art cited by the Examiner in support of the claim rejections under 35 U.S.C. §103. Specifically, the controlled-release composition defined by claim 1 of US 6,245,351 to Nara et al. ("Nara") is defined by a "drug-containing core". For all of the foregoing reasons, the nature of the core material of the claimed invention is not indefinite. Applicant should not be required to limit the claimed invention to one type of or one method of preparing the core material, e.g., from a starter seed (See claim 6).

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 7 of 14

The claimed dosage form also comprises a semipermeable membrane comprising a single polymer composition containing a modifying agent and a water insoluble polymer selected from the group consisting of cellulose ethers, cellulose esters, polyvinyl esters and acrylic polymers. Applicants submit that the phrase "a single polymer composition" as used in claim 1 can only be interpreted to mean that the semipermeable membrane contains only one polymer, i.e., a water insoluble polymer, notwithstanding the fact that claim 1 is open-ended by reason of the transitional phrase "comprising". At page 8, lines 4-9, the specification describes the semipermeable membrane as containing a water-insoluble polymer and a modifying agent. This disclosure comports with Example 3 showing the preparation of a semipermeable membrane containing one water-insoluble polymer and one modifying agent. In contrast, the specification uses the expression "one or more" when more than just one alkaline agent and/or swelling agent can be used in the preparation of the core material (See page 3, lines 15-23; claim 1). Furthermore, to distinguish the claimed invention over Nara, Applicants have repetitively argued that single polymer coating composition of the claimed invention is distinguishable from the two or three polymer coating composition taught by Nara. Therefore, based on the claim language, the written description, examples and prosecution history, the phrase "a single polymer" is properly construed to mean that the semipermeable contains only one polymer. *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 977-79 (Fed. Cir. 1999).

Claim 1 has been amended to clarify the structure of the claimed dosage form. As disclosed in the specification at page 5, line 26, the core material is in the form of pellets, spheroids or small tablets. The core material is layered with a sufficient amount of the semipermeable membrane composition to cover the core material (See p. 8, lines 24-25). The core material coated with the semipermeable membrane is filled into a capsule or optionally mixed with tablet excipients and compressed into a multiple unit tableted dosage form (See p. 9, lines 3-5).

The semipermeable membrane is able to disrupt and it is the outermost layer covering the core material. Support is provided by the Figures 1-4. Applicants submit that a gelatin capsule is not the structural or functional equivalent of an outermost layer of a semipermeable membrane covering the core material. Firstly, a gelatin capsule is not able to disrupt but dissolves in the stomach to release its contents. Secondly, the claimed invention requires that a sufficient amount

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 8 of 14

of the semipermeable membrane composition layer and cover the core material. A gelatin capsule encloses and contains its multiple unit contents, e.g., pellets, but does not layer and cover each multiple unit as required by the claimed invention.

Finally, the dosage form is not enteric coated.

Applicants submit that no new matter has been introduced by the claim amendments.

IV. Claim Rejections – 35 U.S.C. §103(a)

A. US 6,245,351 to Nara et al. ("Nara") in view of US 5,753,265 to Bergstrand et al. ("Bergstrand")

Claims 1, 3, 6-8, 12-18, 20 and 25-29 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Bergstrand.

On page 2 of the Advisory Action, the Examiner states that the "only difference [between the claimed invention and Nara] is that the swellable polymer and the water insoluble polymer of the present invention are coated onto the core in 2 separate steps...while the swellable polymer and the water insoluble polymer taught by Nara are combined and then coated onto the core in alone single step."

At a minimum, the method of the claimed invention, as illustrated by claim 20, and that of Nara, as illustrated by claim 21, require two separate steps: a first step for preparing the core material and a second step for coating the core material.

	Claimed Invention	Nara
Step 1	prepare core containing the active, one or more alkaline additives, one or more swelling agents	prepare drug-containing core
Step 2	coat core with a single polymer composition containing a modifying agent and a water insoluble polymer	coat core with a two polymer composition containing a water insoluble polymer and a swellable polymer

Therefore, the number of steps for coating the core is not a useful basis for understanding the patentable differences between the claimed invention and Nara. Rather, it is the inclusion of the swelling agent in the core material *only* and not also in the semipermeable membrane that distinguishes the claimed invention from Nara. It is the interaction between the swellable agent-containing core and the single polymer composition that brings about the

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 9 of 14

disruption of the semipermeable membrane following expansion of the swelling agent upon contact with moisture and built-up pressure in the core (p. 4, lines 16-19).

In contrast, the swellable polymer and an optional plasticizer are present in the coating composition taught by Nara. (See col. 6, lines 54-55). In all but one working example, Nara teaches the inclusion of an appropriate amount of a plasticizer in the coating composition (See Examples 1-3 and 5-11). Applicants submit that the presence of the swellable polymer and plasticizer in the coating composition underscore Nara's failure to teach or suggest a semipermeable membrane that is able to disrupt as expressly required by the claimed invention. The plasticizer renders the coating composition more flexible and resistant to changes in pressure within the dosage form following administration, which changes could have an undesirable impact on the release profile of the active. As such, Nara teaches away from the claimed invention.

At the bottom of page 2 of the Advisory Action, it is stated that "the Examiner is unable to determine the unexpected result of an omeprazole core coated with a water insoluble polymer and a swellable polymer in two separate coating steps, over the coating of the same ingredient in a single coating solution". On the question of obviousness, Applicants submit that it is more pertinent to ask what is the advantage of the interaction between the swellable agent-containing core and the single polymer composition of the claimed invention in comparison to the coating composition taught by Nara which contains two or three polymers, including the swellable polymer.

Nara provides dissolution data only for Examples 1 and 9. Specifically, Experimental Example 1 used the composition obtained in Example 1 and the test results are shown in Figure 1 (See col. 13, lines 4-23). Experimental Example 2 used the composition obtained in Example 9 and the test results are shown in Figure 2 (See col. 13, lines 24-38). A summary of the coating composition of Examples 1 and 9 are provided in the following table:

Serial No. 09/646,852, filed 22 September 2000
 Docket No. 1103326-0636
 Page 10 of 14

RECEIVED
 CENTRAL FAX CENTER

JUN 12 2008

	Example 1	Example 9
separating layer	HPMC	HPMC
3 polymer coating composition	<ul style="list-style-type: none"> • ethyl cellulose as the water insoluble polymeric component; • Carbomer/HIVISWAK as the water soluble, swellable polymer; and • HPMC as the hydrophilic polymer. 	<ul style="list-style-type: none"> • ethyl cellulose as the water insoluble polymeric component; • Carbomer/HIVISWAK as the water soluble, swellable polymer; and • HPMC as the hydrophilic polymer
Plasticizer	YES	YES

Example 4 of the application provides dissolution data obtained with coated pellets prepared in accordance with the claimed invention, i.e., no separating layer and a single polymer coating composition without a plasticizer. Dissolution of the active substance was tested by first immersing the coated pellets in an acid medium for two hours and then adding buffer components to change the pH to 6.8. The results appear on page 14 of the specification and are reproduced as follows:

TIME (hours) (after 2 hours of pre-exposure in acid medium)	% release of active ingredient
0.5	3
1	18
2	60
3	73

Figure 1 of Nara shows that only about 40% of the active of the composition of Example 1 was released (pH 6.8) after five hours. In contrast, the dissolution data provided by Example 4 of the application, i.e., after 2 + 3 hours, is 33% better than that of Example 1 (Figure 1) of Nara.

Figure 2 of Nara is noteworthy for its disclosure of a rapid dissolution rate of the drug at pH 1.2 and 6.8. Specifically, Figure 2 shows that about 10% of the drug was released after two hours at pH 1.2. In contrast, Example 4 of the subject application at page 13, lines 11-15, reports that 96% of the drug remained in the claimed dosage form (pellets) when tested for gastric acid resistance by immersing pellets in 0.1M HCl for two hours. One possible explanation is that a

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 11 of 14

maximum of 4% of the drug leached out of the test samples. For an acid-labile drug such as an omeprazole compound, it is extremely important to minimize the amount of leaching while the dosage form passes through the acidic environment of the stomach, especially since the dosage form is not protected by an enteric coat. Leaching or rapid release is undesirable since omeprazole and its related compounds are rapidly destroyed in media having a low pH. Advantageously, therefore, the claimed invention combines rapid dissolution at pH 6.8 with a very low dissolution (4% vs. 10%) in pH 1.2, a combination which Nara fails to achieve or suggest as shown by Figure 2.

Furthermore, the claimed invention provides a dosage form that is a cost-effective improvement over Nara. Due to the interaction between the swellable agent-containing core and the single polymer composition of the claimed invention, it is possible to avoid the need for a separating layer and eliminate other ingredients without sacrificing the release profile and efficacy of the final dosage form. In fact, the release profile of the claimed invention represents a superior unexpected result: low dissolution at pH 1.2 combined with rapid dissolution at pH 6.8.

For all of the foregoing reasons, Applicants submit that Nara fails to suggest the function and structure of the claimed dosage form comprising a core material coated with an outer layer, wherein the outermost layer is a semipermeable membrane comprising a single polymer composition containing a water insoluble polymer and a modifying agent, and wherein the semipermeable agent is able to disrupt.

The Examiner relies on the secondary reference to Bergstrand of an enteric-coated tablet core having an optional separating layer that is applied onto the core material before applying the enteric coating layer(s). Bergstrand discloses that the optional separating layer is prepared from pharmaceutically acceptable compounds, such as those disclosed at column 7, lines 57-63, whether used alone or in mixtures. The optional separating layer may include additives such as plasticizers, colorants, pigments, fillers, anti-tacking and antistatic agents (col. 7, lines 63-67).

The Examiner alleges that it would be obvious at the time the claimed invention was made to combine Nara and Bergstrand to arrive at the claimed invention. Applicants respectfully disagree.

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 12 of 14

Claim 1 has been amended to clarify that the outermost layer of the claimed invention is the semipermeable membrane comprising a single polymer composition. The primary reference to Nara fails to disclose or suggest any such outermost coating comprising a single polymer coating composition. Rather, Nara discloses an optional separating layer comprising a single polymer such as ethyl cellulose to separate the drug from the coating composition. (See col. 6, lines 4-10; and Example 11). As disclosed at column 6, lines 4-10 and Example 11, the separating layer is then overcoated with a coating composition comprising the two or three polymers as described above. There is no disclosure by Nara that a dosage form having an optional separating layer but not an overcoat of the coating composition is intended for administration.

For all of the foregoing reasons, Applicants submit that Bergstrand fails to overcome the deficiencies of Nara to suggest the function and structure of the claimed dosage form. Whether taken alone or in combination, neither Nara nor Bergstrand suggests the claimed dosage form comprising a core material coated with an outermost layer of a semipermeable membrane comprising a single polymer composition containing a water insoluble polymer and a modifying agent, and wherein the semipermeable agent is able to disrupt.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Accordingly, withdrawal of the §103 rejection of claims 1, 3, 6-8, 12-18, 20 and 25-29 based on the combination of Nara and Bergstrand is requested.

B. Nara, Bergstrand and US 5,225,202 to Hodges et al. ("Hodges")

Claims 30 and 31 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Bergstrand and Hodges.

The Examiner relies on the disclosure by Hodges of an enteric-coated tablet core containing the active and a buffering agent within the range of from about 1 to about 20% by weight (col. 3, lines 20-26). The Examiner concludes, therefore, that it would have been obvious to use an alkaline additive in an amount taught by Hodges to obtain a stable acid-labile composition.

Claims 30 and 31 are directly dependent on claim 1. For all of the reasons given in Section IV(A), above, there would have been no motivation at the time the claimed invention

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 13 of 14

was made to combine Nara and Bergstrand to arrive at the claimed invention, for example as defined by claim 1. Hodges does not overcome the failure of the combination of Nara and Bergstrand to establish a *prima facie* case of obviousness. Accordingly, withdrawal of the §103 rejection of claims 30 and 31 is requested.

**C. Nara, Bergstrand and US 4,795,644 to Zentner ("Zentner") or
US 6,013,281 to Lundberg et al. ("Lundberg")**

Claims 9 and 10 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Bergstrand and Zentner or Lundberg.

Zentner is cited by the Examiner for the alleged disclosure of sodium mono- or di-phosphate as a pH modifying agent. Lundberg is cited for the disclosure of arginine as an alkaline reacting compound.

Claims 9 and 10 are directly or indirectly dependent on claim 1. For all of the reasons given in Section IV(A), above, there would have been no motivation at the time the claimed invention was made to combine Nara and Bergstrand to arrive at the claimed invention, for example as defined by claim 1. Neither Zentner nor Lundberg overcomes the failure of the combination of Nara and Bergstrand to establish a *prima facie* case of obviousness. Accordingly, withdrawal of the §103 rejection of claims 9 and 10 is requested.

D. Nara, Bergstrand and WO 98/54171 ("Cotton")

Claims 4, 5 and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nara in view of Bergstrand and Cotton.

As stated by the Examiner on page 8 of the Office Action, Cotton is cited for the disclosure of the magnesium salt of S-omeprazole as an active ingredient. Applicants submit that Cotton does not overcome the deficiencies of Nara and Bergstrand to establish a *prima facie* case of obviousness for the reasons given in Section IV(A). Withdrawal of the §103 rejection of claims 4, 5 and 23-26 is requested.

Serial No. 09/646,852, filed 22 September 2000
Docket No. 1103326-0636
Page 14 of 14

RECEIVED
CENTRAL FAX CENTER

JUN 12 2008


CONCLUSION

Applicants have made a good faith attempt to respond to the Office Action. It is respectfully submitted that claims 1, 3-10, 12-18, 20 and 23-31 are in condition for allowance, which action is earnestly solicited.

Any fees due in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: 12 June 2008

Respectfully submitted,



John M. Genova
Reg. No. 32,224

Customer No. 07470
Direct Dial: (212) 819-8832

Enclosure: Form PTO/SB/30 (1 page)